REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these remarks.

I. Status of the Claims

No claim amendments are proffered. Claims 16, 18-20 and 28-32 are pending.

II. Rejection of Claims under 35 U.S.C. §103(a)

A. Roizman and Vile

The examiner maintained the rejection for alleged obviousness over U.S. Patent No. 6,172,047 to Roizman *et al.* ("Roizman") in view of Vile *et al.*, *Ann. Oncol.* 5 Suppl. 4: 59-65 (1994) ("Vile"). Applicants respectfully traverse the rejection.

(i) Summary of prosecution to date

As detailed in prior responses, Roizman teaches an HSV vector having a mutation in the γ34.5 gene, and Vile teaches exogenous expression of cytokines in tumor cells. During an interview with Examiner Shen and Examiner Ton on July 9, 2009, applicants' representatives emphasized that the prior art considered cytokine expression to be inhibitory of HSV replication, thereby discouraging one of ordinary skill from combining cytokine expression (Vile) with HSV-based oncolytic therapy (Roizman).

As discussed during the interview, the skilled artisan would not have considered it obvious to combine the teachings of the cited references, thereby arriving at the claimed invention; this, because the claimed invention requires both initial infection and replication thereafter of the HSV vector in the host cells, while the conventional wisdom was that cytokine blocked infection and replication of HSV. In the course of that discussion, Examiner Shen invited applicants to submit additional evidence in support of this notion. See page 2 of Interview Summary dated July 14, 2009. Accompanying the response filed on July 20, 2009, therefore, applicants duly submitted Exhibit 1 by Ghiasi *et al.* showing that expression of cytokine IL-2 by HSV results in decreased virus replication, both *in vivo* and *in vitro*.

With this background, applicants were surprised to see, in the pending action, that the examiner still insists that preventive effect of *in situ* cytokine expression on HSV infection of host cells would not have discouraged the skilled artisan because the claimed invention requires cytokine expression only after the initial HSV infection. See final Office Action, page 10, last full paragraph. Even more surprising, the examiner is silent regarding the evidence, which he had requested, to the effect that *in situ* cytokine blocks HSV replication in host even after the initial infection.

By the same token, the post-interview final Office Action, dated November 12, 2009, in no way reflects Examiner Shen's position during the interview. Instead, the examiner now asserts out of the context of the interview: (i) that the efficacy of the claimed HSV in cancer therapy is the "intended use" and therefore is not given patentable weight because the present claims are product claims, (ii) that "eliciting an immune response" is considered an "inherent" property of the cytokine, and (iii) that the HSV strains mentioned in Rabkin Declaration are "not commensurate in scope with the claimed HSV." *Id.,* at pages 3, 7, 11, 12, 15 and 16. Each of these new assertions is addressed below, *seriatim.*

(ii) The examiner improperly invoked "intended use" to substantiate the rejection

The examiner asserts that the "intended use" of the claimed invention for cancer therapy is not given patentable weight because the claims are product claims. However, the claimed invention is directed to an HSV with a characteristic oncolytic property, namely, the ability to infect and lyse cancer cells while leaving normal cells unharmed and expressing a cytokine that can elicit an immune response against a tumor cell. Without question, these cancer therapeutic features are determined by genomic coding, *i.e.*, a defective γ34.5 gene and incorporation of a cytokine gene, which constitutes a fundamental structure of the virus.

Accordingly, the combination of the claimed oncolytic HSV vector with the recited cytokine expression should be given full weight as a patentable distinction over prior-art teachings because such combination was not suggested by the prior art. Indeed, applicants have made declaration evidence of record to the effect that, at the filing time, conventional wisdom actually directed one of ordinary skill away from the notion of expressing cytokines in an

oncolytic vector, such as the recited HSV vector; this is, because certain cytokines were reported to protect the host from HSV infection, which is prerequisite to the operation of an oncolytic vector.

The examiner's discounting of presently recited *structural* (*i.e.*, genomic) features on the grounds of "intended use" is wholly improper, therefore

(iii) The property of the cytokine must be evaluated in the viral context

The examiner relies on Vile for the alleged teaching of tumorigenicity of cytokine. According to the examiner, "eliciting an immune response against a tumor cell" is an "inherent" property of the cytokine. See final Office Action, in the paragraph bridging pages 4 and 5, and at page 7, lines 8 and 9.

In fact, Vile describes: (i) transduction of ***tumor cells in vitro*** with cDNA encoding a cytokine and then returning the cells ***in vivo*** to animal tumor models; and (ii) ***direct injection of naked DNA*** encoding cytokine genes under a Tyr-promoter. See abstract, page 61, left column, and page 63, right column. Neither embodiment teaches or suggests that expressing a cytokine ***in the context of an oncolytic virus*** can achieve cancer therapy effects by eliciting an immune response against cancer cells. Thus, the examiner fails to appreciate that Vile evidences no guidance to the skilled artisan regarding whether a cytokine could be expressed effectively in an oncolytic virus, *i.e.*, in a context where the vector killed host cells. Without sufficient expression of the cytokine in host cells, the property of cytokine of eliciting an immune response cannot be evaluated in a "vacuum."

The examiner contends that the cytokine's protective effect would not have contradicted the goal of tumor therapy because "it is not uncommon that expression of a protein (cytokine, in this case) may result in multiple effects" (final Office Action, paragraph bridging pages 10 and 11). The examiner can make the rejection only by considering the "multiple effects" of cytokine out of context. As repeatedly pointed out in the prior responses, the skilled artisan would have weighed (A) the prospect of inhibiting viral infection and replication against (B) the prospect of eliciting an immune response, when both (A) and (B) are possible cytokine effects, in a context that offered little or no guidance for combining the cited references.

(iv) The vectors used in cited publications are commensurate in scope with the claimed invention

The examiner asserts that none of Exhibits A, C, F and H accompanying the Rabkin Declaration, nor Exhibit 1 submitted with the response filed on July 20, 2009, is commensurate in scope with the claimed mutant HSV expressing a cytokine.

All these publications were submitted in support of the notion that expression of a cytokine resulted in prevention or decreased HSV replication, which is required for the claimed invention. Specifically, Exhibit A shows that IFN-α2 and IFN-β block HSV-1 replication; Exhibit C confirms that TNF and IFNγ have antiviral activities against HSV-1 and HSV-2; Exhibit F discloses that IFN-α B/D is highly effective in preventing viral replication and cell destruction induced by HSV-1; Exhibit H presents that IL-3 markedly inhibits HSV-1 replication in primary mouse embryonic head cell cultures; and Exhibit 1 demonstrates that expression of IL-2 results in decreased HSV-1 replication *in vivo* and *in vitro*.

The examiner disregarded the fact that all viruses used by these references fall into the same category of HSV vectors delineated by the claims, but emphasized that the specific genetic mutations are not exactly the same in the references. Indeed, HSV-1 is the mother virus of the mutant HSV encompassed by the claimed invention. *See* specification at page 1, first paragraph.

The MPEP requires a showing of results commensurate in scope with but not precisely identical to the claim(s) in question. Thus, MPEP § 2145 states that "an exemplary showing may be sufficient to establish ***a reasonable correlation*** between the showing and the entire scope of the claim, when ***viewed by a skilled artisan***" (emphasis added). *See, e.g., In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

In the present case, the viruses demonstrated in the cited publications on HSV-1 are reasonably correlated to the claimed invention when viewed by a skilled artisan because they fall in the same category of HSV, replication of which is necessary for the claimed invention but replication of which is blocked by cytokine expression. In fact, if the examiner is looking for the exactly same viral context, i.e., "a [sic] HSV with null mutation of both γ34.5 and ribonucleotide reductase and a cytokine gene inserted in the HSV genome" (final Office Action, page 12, lines

3-4), such virus was unavailable at the filing date, a "defect" evidencing the novelty and non-obviousness of the claimed invention.

(iii) The unexpected therapeutic effects achieved by the claimed HSV is left unchallenged

The examiner asserts that Vile demonstrates tumorigenicity as cDNAs encoding cytokines were detected *in vivo*. See final Office Action, page 14, first full paragraph. In fact, one skilled in the art would not have drawn the same conclusion from Vile. Vile clearly shows that, although some degree of reduced mRNA is detected by RT-PCR, there is no indication of actual tumor reduction (page 62, right column), possibly leading to significant clinical results. As discussed in the foregoing sections, moreover, Vile's protocol of returning tumor cells in vivo following transduction by a cytokine cDNA or injecting naked DNA encoding a cytokine in no way predicts the therapeutic outcome of the claimed invention, which entails the combination of an oncolytic HSV vector and expression of a cytokine.

B. Roizman, Vile and Chang

Claims 18-20 remain rejected for alleged obviousness over Roizman, Vile and Chang. Applicants respectfully traverse the rejection.

Roizman and Vile are discussed above. Chang is cited for the alleged teaching of an HSV having a mutation in the ribonucleotide reductase gene. Because Chang fails to compensate for the deficiency of Roizman and Vile, the combined teachings of the cited references fail to render the claims obvious.

C. Roizman, Vile, McKay and Wright

Claims 30-32 remain rejected for alleged obviousness over Roizman and Vile in view of McKay and Wright. Applicants respectfully traverse the rejection.

McKay and Wright are cited for the alleged teaching of tumor-specific promoters but fail to remedy the deficiencies of Roizman and Vile as discussed. Therefore, claims 30-32 are non-obvious over the cited art.

In view of foregoing, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

The present application is in condition for allowance, and applicants request an early indication to this effect. Examiner Shen also is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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